

## Original Article

# Active and passive smoking with breast cancer risk for Chinese females: a systematic review and meta-analysis

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## Abstract

Previous studies suggested that smoking and passive smoking could increase the risk of breast cancer, but the results were inconsistent, especially for Chinese females. Thus, we systematically searched cohort and case-control studies investigating the associations of active and passive smoking with breast cancer risk among Chinese females in four English databases (PubMed, Embase, ScienceDirect, and Wiley) and three Chinese databases (CNKI, WanFang, and VIP). Fifty-one articles (3 cohort studies and 48 case-control studies) covering 17 provinces of China were finally included in this systematic review. Among Chinese females, there was significant association between passive smoking and this risk of breast cancer [odds ratio (OR): 1.62; 95% confidence interval (CI): 1.39–1.85;  $I^2 = 75.8%$ ,  $P < 0.001$ ;  $n = 26$ ] but no significant association between active smoking and the risk of breast cancer (OR: 1.04; 95% CI: 0.89–1.20;  $I^2 = 13.9%$ ,  $P = 0.248$ ;  $n = 31$ ). The OR of exposure to husband's smoking and to smoke in the workplace was 1.27 (95% CI: 1.07–1.50) and 1.66 (95% CI: 1.07–2.59), respectively. The OR of light and heavy passive smoking was 1.11 and 1.41, respectively, for women exposed to their husband's smoke (< 20 and  $\geq 20$  cigarettes per day), and 1.07 and 1.87, respectively, for those exposed to smoke in the workplace (< 300 and  $\geq 300$  min of exposure per day). These results imply that passive smoking is associated with an increased risk of breast cancer, and the risk seems to increase as the level of passive exposure to smoke increases among Chinese females. Women with passive exposure to smoke in the workplace have a higher risk of breast cancer than those exposed to their husband's smoking.

**Key words** Systematic review, meta-analysis, active smoking, passive smoking, breast cancer, Chinese females

Chinese females have a lower incidence of breast cancer compared with their counterparts in Western countries. However, the incidence of breast cancer has increased steadily at an alarming rate over the past two decades (from 29.9/100,000 in 1989–1993 to 50.1/100,000 in 2004–2008 in Chinese urban areas, and from 6.5/100,000 to 17.3/100,000 in Chinese rural areas), making breast

cancer the most common and fifth most common cancer for Chinese urban and rural females, respectively<sup>[1]</sup>.

As a country with one of the highest rates of tobacco consumption<sup>[2,3]</sup>, China is one of the most seriously affected countries by tobacco. Nearly 700,000 Chinese died as a result of active smoking in 2005, and another 100,000 deaths were attributable to passive smoking in 2002<sup>[2,3]</sup>. Although the prevalence of active smoking among Chinese females has been low (3.8% in 1996 and 2.4% in 2010), the prevalence of passive smoking in this population has remained high for nearly two decades (approximately 60% between 1996 and 2010)<sup>[4,5]</sup>. Women also bear nearly 80% of the total cancer burden from passive smoking<sup>[3]</sup>.

Although there is no way to completely prevent breast cancer<sup>[6]</sup>, tobacco is considered the most preventable cause of cancer worldwide. Several studies suggest that women who consume tobacco or who were exposed to passive smoking may have an increased risk of breast cancer. However, a collaborative re-analysis of the 53 worldwide epidemiologic studies found that active smoking had little or no independent effect on breast cancer incidence<sup>[7]</sup>.

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Another three large American cohort studies revealed little association between passive smoking and breast cancer risk<sup>[8-10]</sup>. The unclear associations between active or passive smoking and breast cancer risk also exist in China. Until now, there has been no systematic review summarizing current studies on active smoking and breast cancer risk in China. The only systematic review focusing on the associations between passive smoking and breast cancer risk among Chinese females<sup>[11]</sup> missed more than 10 important studies, which would inevitably incur bias in the final conclusion. And this review did not include subgroup analyses (quality of study, sample size, region of China, etc) or any further analysis to explore the different effects of exposure to husband's smoking and to smoke in the workplace.

To shed light on the potential roles of active and passive smoking on the risk of breast cancer among Chinese females, we performed this systematic review and meta-analysis to help resolve these uncertainties.

## Materials and Methods

We conducted this systematic review according to the guideline of meta-analysis of observational studies in epidemiology (MOOSE)<sup>[12]</sup>.

### Searching strategy

Two reviewers independently searched the literature published in four English databases (PubMed, Embase, ScienceDirect, and Wiley) and three Chinese databases (CNKI, WanFang, and VIP) up to June 2013. These searches were complemented by manual searches. Authors of potential literature were contacted when more information or clarification was needed. Three groups of keywords were used in the Chinese databases: (1) case-control study, cohort study, and prospective study; (2) breast cancer, breast carcinoma, breast tumor, breast neoplasm, mammary cancer, mammary carcinoma, mammary tumor, mammary neoplasm; and (3) smoking, tobacco, risk factor, etiology, polymorphism, and susceptibility. Other groups of keywords were also used in the English databases: Chinese, China, and the Han population. In the PubMed database, all keywords were used with Medical Subject Headings (MeSH).

### Eligibility criteria

Cohort studies and case-control studies investigating the associations between active or passive smoking and breast cancer risk among Chinese females were initially reviewed. Studies that reported risk estimates [odds ratios (ORs) or relative risks (RRs)] and 95% confidence intervals (CIs) or cross-table data were included.

The following studies were excluded: (1) case-control study with benign breast disease selected as controls, (2) case-control study with sample size less than 100 in each arm, (3) study with incomplete data of interest, and (4) duplicate publications.

### Study selection and data extraction

Two review authors, working independently and in parallel,

scanned the abstracts for information concerning the association between active or passive smoking and breast cancer risk, and obtained the full texts of the studies when necessary. After obtaining the full texts, the review authors independently assessed the eligibility of the studies. In the case of multiple publications or overlapping data sets, only studies with the largest or the most updated results were included.

Information on the baseline characteristics (type of study, year of publication, first author, sample size in each arm, and region of China), the methodologic quality of study, and the risk estimates (ORs or RRs) and their 95% CIs or cross-table data were collected. ORs calculated from both the univariate and multivariate logistic regression models were used in the final analysis.

Any disagreement in study selection and data collection was adjudicated by a third reviewer.

### Assessment of the methodologic quality of study

The methodologic quality of observational study was independently assessed by two reviewers according to Newcastle-Ottawa Scale (NOS) based on three broad perspectives<sup>[13]</sup>: (1) the selection of the study groups, (2) the comparability of the groups, and (3) the ascertainment of exposure or outcome of interest. All studies were finally divided into three groups based on NOS scores: scores of 8–9, 5–7, and 0–4. To minimize the bias due to the judgment of NOS, any disagreement in this assessment was adjudicated by a third reviewer.

### Statistical analysis

First, for studies with cross-table data, the ORs and 95% CIs were calculated based on these cross tables. Second, the ORs and 95% CIs calculated from the cross tables were combined with ORs and 95% CIs calculated from univariate logistic regression, which was performed for studies only reporting these data but not cross-table data. Finally, overall ORs and 95% CIs were calculated from all of these ORs and 95% CIs using a random-effect model weighted with the inverse of the variance.

The  $I^2$  statistic was calculated to determine the size of heterogeneity<sup>[14]</sup>. Potential publication bias was assessed with the Egger tests and represented graphically with funnel plots of the OR versus its standard error<sup>[15]</sup>. Pre-specified subgroup meta-analyses were used to explore potential sources of heterogeneity according to type of study, NOS scores, sample size ( $\geq 400$  vs.  $< 400$ ), year of publication ( $\geq 2007$  vs.  $< 2007$ ), and regions of China.

Sensitivity analyses on studies reporting multivariate adjusted ORs were conducted to explore the effect of the potential confounding factors. Sensitivity analyses were also conducted to test whether the primary results were affected by the studies that fell outside of the funnel plot.

Additional analyses were conducted to explore whether (1) breast cancer risk differed between exposure to husband's smoking and to smoke in the workplace and (2) the risk of breast cancer increased as the exposure of passive smoking increased. After summarizing the

definition of light and heavy passive smoking in the included studies, light and heavy passive smoking as a result of husband's smoking were defined here as < 20 cigarettes per day and  $\geq$  20 cigarettes per day, respectively, and light and heavy passive smoking as a result of exposure in the workplace were defined here as < 300 min per day and  $\geq$  300 min per day, respectively.

All the statistical analyses were performed with STATA 12.0. *P* values < 0.05 were considered significant in all tests except the heterogeneity test (*P* < 0.10).

## Results

A total of 56 articles were initially identified as case-control

studies or cohort studies reporting association between active or passive smoking and breast cancer risk among Chinese females<sup>[16-71]</sup>. After discarding five duplicate publications<sup>[67-71]</sup>, 51 articles covering 17 provinces of China were finally included in this systematic review, including 3 cohort studies<sup>[35,42,54]</sup> and 48 case-control studies. There were 21 articles focusing on active smoking only, 19 articles on passive smoking only, and 11 articles on both active and passive smoking (**Table 1**).

### Overall association of active and passive smoking with breast cancer risk

As shown in **Figure 1**, the overall OR of active and passive

**Table 1. Characteristics of included studies on the relationship between active or passive smoking and breast cancer**

Reference	Authors	Year of publication	Region of China	Study design	Number of cases	Number of controls	NOS <sup>a</sup>	Included <sup>b</sup>
[16]	Lu <i>et al.</i>	1992	Shanghai	Case-control	552	552	B	2
[17]	Liu <i>et al.</i>	1994	Guangdong	Case-control	125	250	B	3
[18]	Ye <i>et al.</i>	1995	Anhui	Case-control	100	100	B	3
[19]	Lai <i>et al.</i>	1996	Taiwan	Case-control	114	228	B	1
[20]	Xu <i>et al.</i>	1997	Hebei	Case-control	101	101	B	1
[21]	Yang <i>et al.</i>	1997	Taiwan	Case-control	244	450	B	1
[22]	Liu <i>et al.</i>	1998	Chongqing	Case-control	155	155	B	3
[23]	Tan <i>et al.</i>	1998	Hunan	Case-control	146	146	B	3
[24]	Wei <i>et al.</i>	1998	Heilongjiang	Case-control	160	320	B	1
[25]	Huang <i>et al.</i>	1999	Taiwan	Case-control	150	150	A	1
[26]	Zhao <i>et al.</i>	1999	Sichuan	Case-control	265	265	B	2
[27]	Liu <i>et al.</i>	2000	Chongqing	Case-control	186	186	B	3
[28]	Zhu <i>et al.</i>	2000	Jiangsu	Case-control	116	116	B	3
[29]	Cao <i>et al.</i>	2001	Guangdong	Case-control	348	348	B	3
[30]	Lin <i>et al.</i>	2001	Shandong	Case-control	186	186	B	3
[31]	Zha <i>et al.</i>	2001	Guangdong	Case-control	352	352	B	3
[32]	Zou <i>et al.</i>	2002	Hubei	Case-control	112	112	B	2
[33]	Shrubsole <i>et al.</i>	2004	Shanghai	Case-control	1,459	1,556	A	3
[34]	Louis <i>et al.</i>	2005	Hongkong	Case-control	198	358	B	1
[35]	Shannon <i>et al.</i>	2005	Shanghai	Cohort	378	1,070	A	3
[36]	Chou <i>et al.</i>	2006	Taiwan	Case-control	146	285	B	1
[37]	Huang <i>et al.</i>	2006	Guangdong	Case-control	133	133	B	2
[38]	Li <i>et al.</i>	2006	Sichuan	Case-control	104	154	B	1
[39]	Li <i>et al.</i>	2006	Sichuan	Case-control	121	211	B	1
[40]	Li <i>et al.</i>	2006	Liaoning	Case-control	449	363	B	1
[41]	Wang <i>et al.</i>	2006	Zhejiang	Case-control	101	101	B	3
[42]	Wang <i>et al.</i>	2006	Zhejiang	Cohort	84	269	A	2
[43]	Jin <i>et al.</i>	2007	Jiangsu	Case-control	206	214	B	2
[44]	Li <i>et al.</i>	2007	Hebei	Case-control	175	175	B	3
[45]	Ma <i>et al.</i>	2007	Shandong	Case-control	105	100	B	1
[46]	Lin <i>et al.</i>	2008	Zhejiang	Case-control	237	237	B	3
[47]	Ren <i>et al.</i>	2008	Liaoning	Case-control	200	200	B	3
[48]	Nie <i>et al.</i>	2009	Yunnan	Case-control	200	200	B	1
[49]	Wang <i>et al.</i>	2009	Chongqing	Case-control	367	367	B	1
[50]	Zhang <i>et al.</i>	2009	Guangdong	Case-control	438	438	B	2
[51]	Zhang <i>et al.</i>	2009	Zhejiang	Case-control	1,009	1,009	B	3
[52]	Qian <i>et al.</i>	2010	Jiangsu	Case-control	698	813	B	1

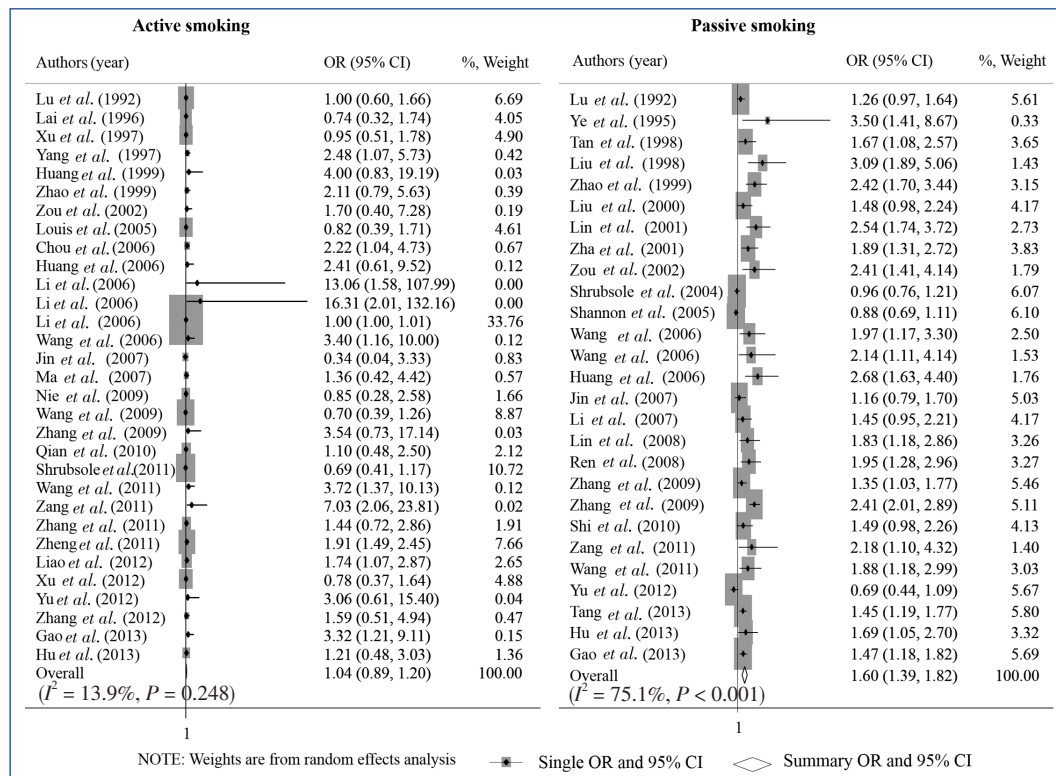
(To be continued)

**Table 1. Characteristics of included studies on the relationship between active or passive smoking and breast cancer (continued)**

Reference	Authors	Year of publication	Region of China	Study design	Number of cases	Number of controls	NOS <sup>a</sup>	Included <sup>b</sup>
[53]	Shi <i>et al.</i>	2010	Jiangsu	Case-control	223	223	B	3
[54]	Shrubsole <i>et al.</i>	2011	Shanghai	Cohort	718	72,519	A	1
[55]	Wang <i>et al.</i>	2011	Shandong	Case-control	150	150	B	3
[56]	Wang <i>et al.</i>	2011	Sichuan	Case-control	400	400	A	1
[57]	Zang <i>et al.</i>	2011	Shandong	Case-control	348	1,044	B	2
[58]	Zhang <i>et al.</i>	2011	Zhejiang	Case-control	1,009	1,009	B	1
[59]	Zheng <i>et al.</i>	2011	Tianjin	Case-control	1,541	1,598	A	1
[60]	Liao <i>et al.</i>	2012	Guangdong	Case-control	285	285	B	1
[61]	Xu <i>et al.</i>	2012	Multi-center	Case-control	416	1,156	B	1
[62]	Yu <i>et al.</i>	2012	Shandong	Case-control	103	309	B	2
[63]	Zhang <i>et al.</i>	2012	Zhejiang	Case-control	252	248	B	1
[64]	Gao <i>et al.</i>	2013	Jiangsu	Case-control	669	682	A	2
[65]	Hu <i>et al.</i>	2013	Hubei	Case-control	196	211	B	2
[66]	Tang <i>et al.</i>	2013	Guangdong	Case-control	839	863	B	3

<sup>a</sup>NOS, Newcastle-Ottawa scale. A, NOS scores 8–9; B, NOS scores 5–7; C, NOS scores 1–4.

<sup>b</sup>1, only included in the meta-analysis of active smoking with breast cancer; 2, included in the meta-analysis of both active and passive smoking with breast cancer; 3, only included in the meta-analysis of passive smoking with breast cancer



**Figure 1. Forest graph on the association of active and passive smoking with breast cancer risk. Each row in the forest graph represents the original odds ratio (OR) with 95% confidence interval (CI) reported in one study. And the last row represents the overall association of active and passive smoking with breast cancer risk.**

smoking with breast cancer risk was 1.04 (95% CI: 0.89–1.20;  $I^2 = 13.9\%$ ,  $P = 0.248$ ;  $n = 31$ ) and 1.62 (95% CI: 1.39–1.85;  $I^2 = 75.8\%$ ,  $P < 0.001$ ;  $n = 26$ ), respectively. The funnel plots showed no evidence of publication bias among the included studies on passive smoking (Egger test,  $P = 0.166$ ), but there might be publication bias among those on active smoking (Egger test,  $P = 0.001$ ; **Figure 2**).

**Association of active and passive smoking with breast cancer risk for different subgroups**

As shown in **Figure 3**, there was a significant association between passive smoking and risk of breast cancer in case-control studies (OR: 1.66; 95% CI: 1.42–1.90) but not in cohort studies, and in

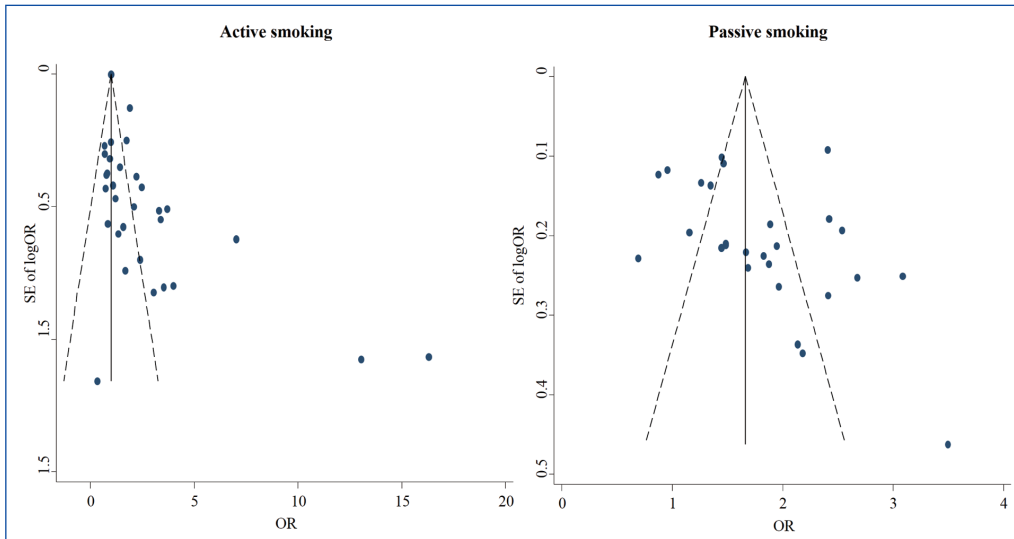


Figure 2. Funnel plots on the association of active and passive smoking with breast cancer risk. Each plot represents the original OR against its standard error of OR reported in one included study. The full line in the middle and the imaginary lines in the two sides represent the overall OR with 95% CI.

Subgroups	Active smoking				Passive smoking			
	OR (95% CI)	n	I <sup>2</sup>	P <sub>heterogeneity</sub>	OR (95% CI)	n	I <sup>2</sup>	P <sub>heterogeneity</sub>
Design of study								
Cohort	1.12 (-0.82, 3.05)	2	30.3	0.231	1.29 (0.25, 2.33)	2	74.2	0.049
Case-control	1.08 (0.92, 1.23)	29	10.2	0.309	1.64 (1.42, 1.86)	25	72.0	<0.001
NOS scores								
8–9	1.68 (0.63, 2.73)	6	73.4	0.002	1.15 (0.82, 1.47)	4	76.3	0.005
5–7	1.00 (1.00, 1.01)	25	0.0	0.937	1.71 (1.46, 1.95)	23	68.0	<0.001
Sample size								
≥ 400	1.08 (0.88, 1.28)	22	33.8	0.063	1.87 (1.57, 2.16)	11	3.0	0.414
< 400	0.95 (0.50, 1.40)	9	0.0	0.928	1.45 (1.21, 1.70)	16	80.8	<0.001
Year of publication								
≥ 2007	1.15 (0.82, 1.49)	17	41.2	0.039	1.53 (1.25, 1.81)	13	73.5	<0.001
< 2007	1.00 (1.00, 1.01)	14	0.0	0.885	1.71 (1.37, 2.04)	14	74.9	<0.001
Region of China								
Jiangsu	1.00 (0.16, 1.84)	3	0.0	0.373	1.38 (1.14, 1.62)	3	0.0	0.520
Shandong	1.64 (-0.26, 3.55)	3	0.0	0.560	1.73 (0.68, 2.78)	4	83.8	<0.001
Shanghai	0.80 (0.49, 1.11)	2	0.0	0.351	1.00 (0.80, 1.19)	3	45.6	0.159
Zhejiang	1.55 (0.61, 2.50)	3	0.0	0.698	2.24 (1.89, 2.60)	4	0.0	0.626
Guangdong	1.79 (0.91, 2.66)	3	0.0	0.878	1.54 (1.23, 1.85)	4	36.1	0.195
Other	1.07 (0.84, 1.29)	17	31.5	0.105	1.81 (1.50, 2.11)	9	7.0	0.377

NOTE: Weights are from random effects analysis    n: number of studies    ◇ Summary OR and 95% CI

Figure 3. Association of active and passive smoking with breast cancer risk for different subgroups. Each diamond represents the overall OR with 95% CI for the specific subgroups studies.

studies with NOS score of 5–7 (OR: 1.75; 95% CI: 1.47–2.02) but not in studies with a higher NOS score. Both the studies with sample size larger or equal to and less than 400 revealed a significant association of passive smoking with breast cancer risk, with an OR of 1.44 (95% CI: 1.17–1.70) and 1.87 (95% CI: 1.59–2.14), respectively. And studies either published in and after 2007 or before 2007 also observed a significant association of passive smoking with breast cancer risk, with an OR of 1.55 (95% CI: 1.23–1.88) and 1.71 (95%

CI: 1.37–2.04), respectively. Although there was no significant association of passive smoking with breast cancer risk in studies conducted in Shandong or Shanghai, the significant association was observed in studies conducted in Jiangsu, Zhejiang, and other regions of China, with an OR of 1.38 (95% CI: 1.14–1.62), 2.24 (95% CI: 1.89–2.60), and 1.76 (95% CI: 1.49–2.03), respectively. No significant associations between active smoking and breast cancer risk were found in subgroup analyses.

**Association of active and passive smoking with breast cancer risk after adjusting for potential confounding factors**

A total of 6 and 12 studies reported adjusted ORs of breast cancer risk with active and passive smoking, respectively. The overall

OR based on these adjusted ORs was 0.95 (95% CI: 0.00–2.02) for active smoking and 1.59 (95% CI: 1.34–1.83) for passive smoking (Figure 4). After excluding studies that fell outside of the funnel plot in the primary analyses, the overall OR was 1.00 (95% CI: 1.00–1.01) for active smoking and 1.62 (95% CI: 1.43–1.80) for passive smoking (Figures 5 and 6). No significant heterogeneity was found among

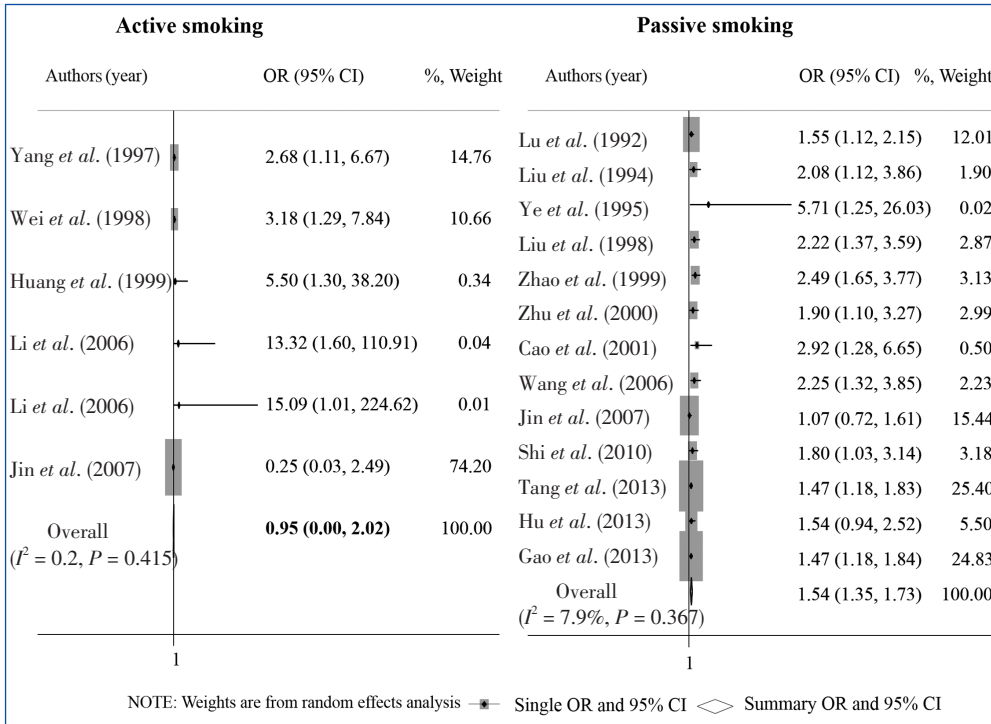


Figure 4. Forest graph on the association of active and passive smoking with breast cancer risk after adjusting for potential confounding factors. Each row in the forest graph represents the original odds ratio (OR) with 95% confidence interval (CI) reported in one study. The diamond in the last row represents the overall OR with 95% CI.

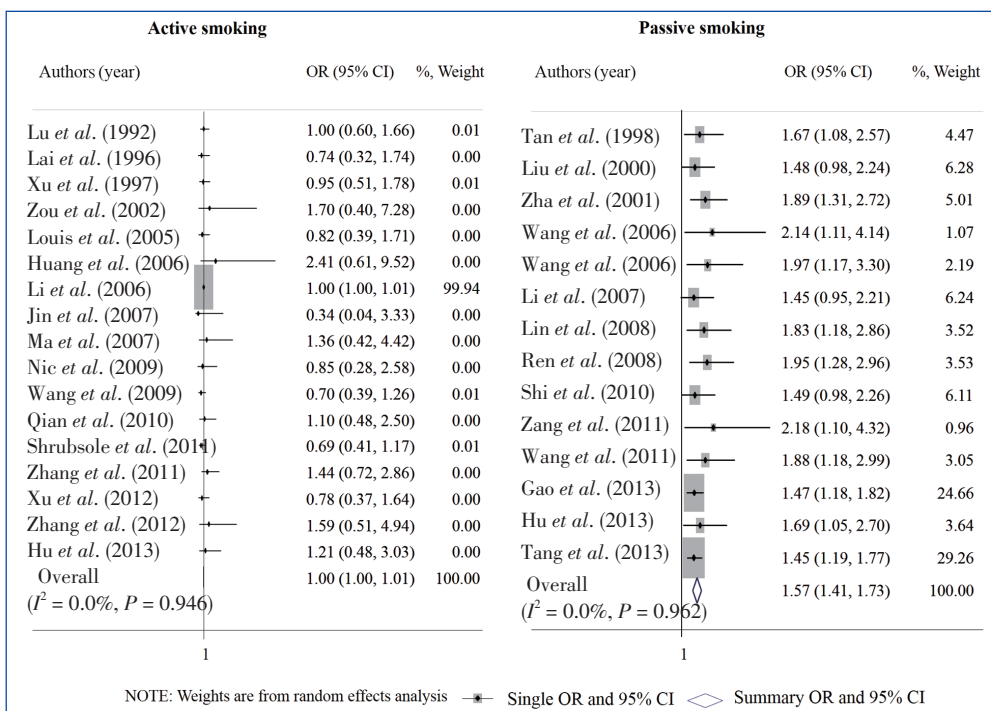


Figure 5. Sensitivity analysis after excluding studies that fell outside of the funnel plots in the primary meta-analysis on the association of active and passive smoking with breast cancer risk. Each row in the forest graph represents the original OR with 95% CI reported in one study. The diamond in the last row represents the overall OR with 95% CI.

these sensitivity analyses.

**Association between passive smoking and breast cancer risk for different sources and levels of exposure**

Additional analyses showed that breast cancer risk was significantly associated with passive exposure to husband's smoking ( $n = 9$  studies) and to smoke in the workplace ( $n = 4$  studies), with overall OR of 1.27 (95% CI: 1.07–1.50) and 1.66 (95% CI: 1.07–2.59), respectively (Figure 7). Further additional analysis showed that the OR of light and heavy passive smoking was 1.11 (95% CI:

0.98–1.25) and 1.41 (95% CI: 0.95–2.09) for women exposed to their husband's smoking ( $< 20$  and  $\geq 20$  cigarettes per day), and 1.07 (95% CI: 0.78–1.48) and 1.87 (95% CI: 0.94–3.72) for those exposed to smoke in the workplace ( $< 300$  and  $\geq 300$  min of exposure per day), respectively (Figure 8).

**Discussion**

The present study suggests that Chinese females exposed to secondhand smoke have an increased risk of breast cancer, and the risk seems to increase as the level of passive exposure to smoke increases. Furthermore, women passively exposed to smoke in the

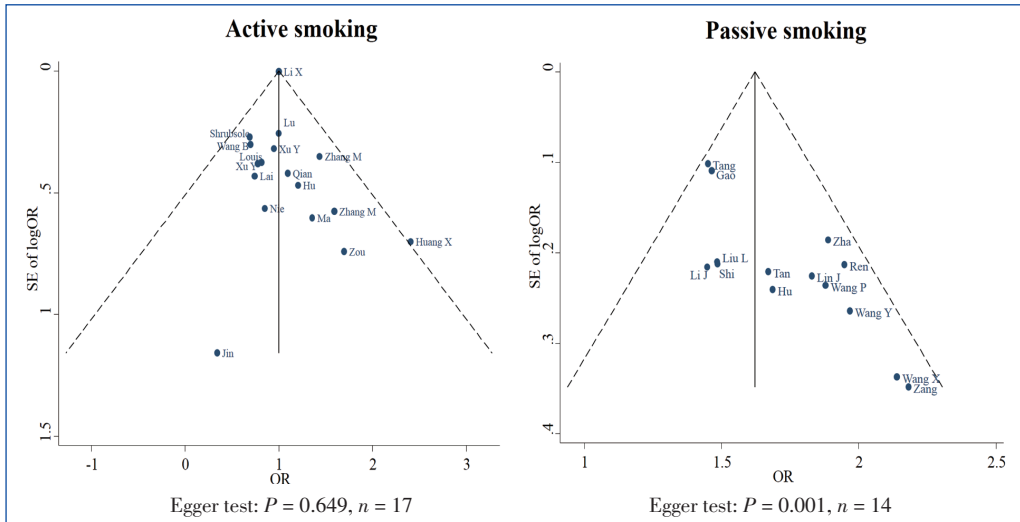


Figure 6. Funnel plots based on sensitivity analysis after excluding studies that fell outside of the funnel plots in the primary meta-analysis on the association of active and passive smoking with breast cancer risk. Each plot represents the original OR against its standard error of OR reported in one included study. The full line in the middle and the imaginary lines in the two sides represent the overall OR with 95% CI.

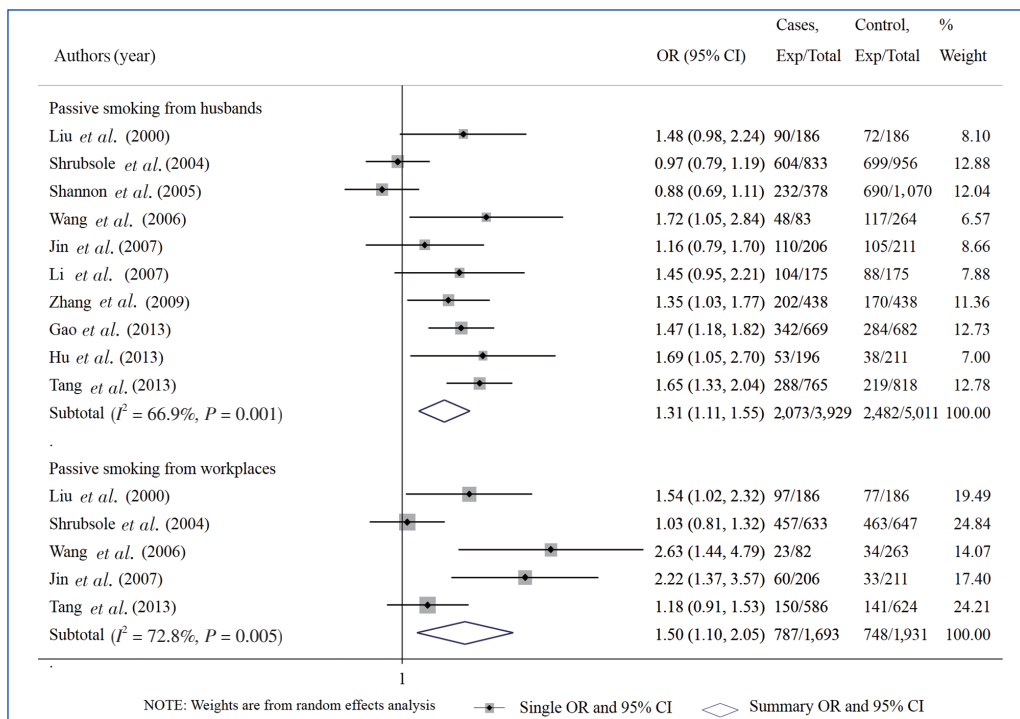


Figure 7. Forest graph on the association of passive smoking with breast cancer risk according to exposure to husband's smoking or to the smoke of workplace. Each row in the forest graph represents the original OR with 95% CI reported in one study. The diamond in the last row represents the overall OR with 95% CI.

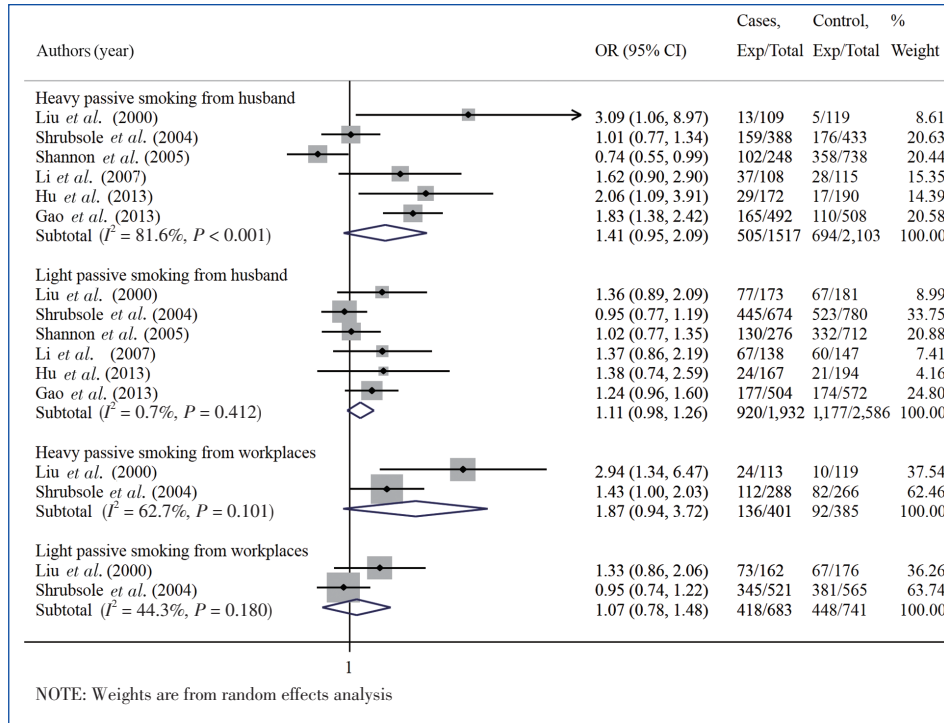


Figure 8. Forest graph on the association of passive smoking with breast cancer risk for different sources and levels of exposure. Each row in the forest graph represents the original OR with 95% CI reported in one study. The diamond in the last row represents the overall OR with 95% CI.

workplace had a higher risk of breast cancer than those exposed to their husband’s smoking in the home.

Our main findings were consistent with those in several previous studies, but three large American cohort studies revealed a negative association between passive smoking and breast cancer risk<sup>[8-10]</sup>. Although cohort studies were generally considered superior to case-control studies because they avoided recall bias, they have serious limitations<sup>[72]</sup>. The potential primary cause for the non-significant associations in the three cohort studies was substantial exposure misclassification: women with regular passive exposure to smoke may have been categorized in the unexposed group<sup>[72]</sup>. This misclassification induced bias and underestimated the association of passive smoking with breast cancer risk. Specifically, in two of the three American cohort studies, passive exposure to smoke was either based exclusively on the husband’s smoking history<sup>[8]</sup> or household exposure<sup>[10]</sup>, and thus women who were exposed to others’ smoking or had occupational exposure to smoke were misclassified as unexposed. In the third cohort study<sup>[9]</sup>, the exposure measure was based on women’s self-reported passive exposure to smoke and ignored historical exposure (including exposure from the 32.6% of husbands who were former smokers, historic workplace exposure, and all childhood exposure).

This misclassification bias may also be the most important reason why we did not observe significant association between passive smoking and breast cancer risk based on cohort studies. In Shannon’s cohort (from Shanghai)<sup>[35]</sup> and Gao’s study<sup>[64]</sup>, passive smoking was based exclusively on the husband’s smoking history. In Wang’s cohort<sup>[42]</sup> and Shrubsole’s study (from Shanghai)<sup>[33]</sup>, sources of passive exposure to smoke only included the husband’s smoking within the household but ignored exposure to smoke from other

sources and exposure during childhood. As these four studies had NOS scores of 8–9 and two were studies conducted in Shanghai, the additional and subgroup analyses did not produce significant results among studies with NOS scores of 8–9 and studies conducted in Shanghai.

Additionally, high passive exposure to smoke in the control group might be another important determinant of the observed non-significant associations in the subgroup analyses. In fact, in several studies, more than 50% of females in the control group were passively exposed to smoke, including studies reported by Shrubsole *et al.*<sup>[33]</sup> (80%), Zha *et al.*<sup>[31]</sup> (72%), Lu *et al.*<sup>[16]</sup> (69%), Shannon *et al.*<sup>[35]</sup> (64%), Yu *et al.*<sup>[62]</sup> (59%), Ren *et al.*<sup>[47]</sup> (58%), and Wang *et al.*<sup>[42]</sup> (51%). As argued by Brind for studies on induced abortion in China, once the prevalence of a given exposure rises to a level of predominance in the control group, statistical adjustment cannot remove all confounding effects caused by the adjustment terms.

Consistent with the collaborative re-analysis of the worldwide evidence from 53 epidemiological studies<sup>[7]</sup>, we found active smoking had no or little effects on the risk of breast cancer. There might be several reasons for the non-significant association of active smoking with breast cancer risk. First, breast cancer caused by smoking was theoretically associated with long latency period of exposure, nearly 30 years or more<sup>[66,74]</sup>. However, in most included studies, the observation intervals were not long enough to ascertain breast cancer, which underestimated the real effects of smoking on breast cancer risk. Second, potential confounders, especially alcohol drinking, greatly attenuated the real association between active smoking and breast cancer risk. As we knew, smokers generally drink more alcohol than non-smokers, and alcohol intake may also be associated with breast cancer risk<sup>[7]</sup>. Although we conducted sensitivity analyses



based on the adjusted OR, it is possible that residual confounding effects could still attenuate the association between active smoking and breast cancer risk. Third, the small prevalence of female smokers in China, such as 0.46% in Zhang *et al.*<sup>[50]</sup>, 0.65% in Li *et al.*<sup>[38]</sup>, 0.73% in Gao *et al.*<sup>[64]</sup>, and 0.97% in Yu *et al.*<sup>[62]</sup>, may also limit the power of finding a significant association between active smoking and breast cancer risk. Finally, active smoking in most studies was self-reported, which might also attenuate the possible association between active smoking and breast cancer risk.

Although the present study revealed non-significant association between active smoking and breast cancer risk, active smoking still warrants attention. Tobacco smoke contains over 7,000 chemicals including 69 established carcinogens, 20 of which are known mammary carcinogens<sup>[47]</sup>. There is also strong evidence that many of these carcinogens can reach mammary tissue<sup>[63]</sup>. Therefore, we still emphasize the importance of smoking cessation and tobacco control.

Our study had several strengths. First, we extended our search strategy to include all potential studies with information on smoking among Chinese females, rather than focusing solely on smoking. Thus, we included more than 10 studies that were excluded in Chen's study<sup>[11]</sup>. Second, we performed several subgroup and sensitivity analyses and found these analyses confirmed the reliability of our primary results. Third, additional analyses helped us to better elucidate the role of active and passive smoking on breast cancer risk. However, because the studies analyzed here did not include passive exposure to smoke from other members within the household, therefore, based on the current evidences, we could only conclude that passive smoking in the workplace poses a greater risk for breast cancer than passive exposure to husband's smoking but not passive smoking in the household.

In addition, there are also several potential limitations to our meta-analysis. First, moderate heterogeneity was observed in the primary analysis for passive smoking, and the heterogeneity was not significantly improved in subgroup analysis. Thus, factors in addition to those listed in the subgroup analysis may influence our results. Second, the current systematic review cannot overcome the limitations of the original studies. Though a detailed protocol with explicit criteria for study selection and strict strategies for data extraction were developed before the study, the limitations in

exposure definitions and population selection in the original will still affect the current results. Third, due to lack of individual information as in other systematic reviews, the current systematic review cannot control the potential confounding bias caused by other genetic and environmental factors of breast cancer, even if the maximum adjusted ORs were used for sensitivity analysis. Fourth, due to inadequate overall power, we observed a borderline but not significant dose-response relationship between the level of passive exposure to smoke and breast cancer risk. Therefore, the current results should be interpreted carefully.

In summary, this study suggests that passive smoking is associated with an increased risk of breast cancer among Chinese females, and the risk seems to increase as passive exposure to smoke increases. Women passively exposed to smoke in the workplace have a higher risk of breast cancer than those passively exposed to their husbands' smoking. If passive smoking were to be confirmed as a risk factor for breast cancer, high rates of passive smoking in China may contribute to increasing breast cancer incidence. Tobacco control, especially in the public places, is urgently needed in China in the future.

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